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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,309	01/03/2001	Christine Andreoni	PF82PCTSEQ/d	7033

25666 7590 11/16/2004

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EXAMINER	
SHAHNAN SHAH, KHATOL S	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 11/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/647,309	ANDREONI ET AL.	
	Examiner	Art Unit	
	Khatol S Shahnan-Shah	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-24 and 26-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-24 and 26-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *10/5 and 10/7 2004*, 1/22/04
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 22-24 and 26-39 are pending and under consideration in this application.

Interview Summary and Withdrawal of Finality

2. On 10/5/04 and 10/7/04 upon telephonic interviews conducted between Attorney Patrick G. Sage (reg # 37710) and Supervisory Examiner Lynette Smith, the SPE stated to the attorney that the advisory and the final actions will be vacated (see attached interview summary) and, therefore, the finality is withdrawn. The examiner is withdrawing finality of previous actions to further develop the prosecution record and further consider applicants' arguments.

Note: The examiner also clarifies on the record that no petition under 37 CFR 1.181 for withdrawal of finality has been submitted by the applicants in this application. On July 30 2004, applicants have submitted a response under 37 CFR 1.116 and in their response they have requested to withdraw finality. Applicants' response on page 1 under the title of the response recites " Response after final under 37 CFR 1.116; Information Disclosure Statement 37 CFR 1.98 and Petition 37 CFR 1.181 for withdrawal of finality". On page 2 of the response applicants made the argument why the finality should be withdrawn. The examiner called Mr. Patrick Sage (applicants' attorney) on September 22, 2004 and inquired if a separate petition was submitted to the office. The attorney said no separate petition has been sent (see attached interview summary).

Prior Citations of Title 35 Sections

3. The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior office action.

Prior Citations of References

4. The references cited or used as prior art in support of one or more rejections in the instant office action have been previously cited and made of record. No form PTO-892 or 1449 have been submitted with this office action.

Rejections Withdrawn

5. Rejection of claims 22-24 and 26-39 under 35 U.S.C. 103 as being obvious over Haeuw et al. in view of Cooper et al. made in paragraph 17 of the office action mailed 4/07/2004 is withdrawn in view of assessment of newly available translated French priority document.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 22-24 and 26- 39 are rejected under 35 U.S.C. 103(a) as being obvious over Rauly et al. (Research in Immunology, Vol. 149, No.1, pp. 99, January 1998) in view of Cooper et al. (Journal of infectious, Vol. 147, No.2, pp. 312-317, February 1983).

Claims are drawn to a method of improving immunity of a mammal with respect to an antigen or a hapten, through intranasal administration of a pharmaceutical composition comprising *Klebsiella pneumoniae* outer membrane protein OmpA having SEQ ID NO 2. combined with the antigen or the hapten.

Note: The examiner interprets the invention as a method of enhancing or improving immunity of a mammal, said method comprising the steps of intranasally administering a pharmaceutical composition (i.e. OmpA of *Klebsiella pneumoniae* coupled to G antigen of RSV) into a mammal.

Rauly et al. teach a method of using an outer membrane protein (OmpA) of *Klebsiella pneumoniae* for enhancing or improving immunity of a mammal with respect to an antigen (see page 99). Rauly et al. teach a protein obtained by recombinant process. Rauly et al. teach use of the G1 antigen of RSV coupled to rP40 protein of *Klebsiella pneumonia,* the same conjugate as the claimed invention. Rauly et al. teach that the conjugate generated strong antibody response even in the absence of any adjuvant. Rauly et al. do not explicitly teach SEQ ID NO: 2.

However, Rauly et al. teach OmpA protein (rP40) of *Klebsiella pneumoniae* having the same name, structural properties, produced from the same organism, in the same institute (Pierre Fabre) by the same group of scientists (Rauly, Haeuw and Baussant). Therefore, it is considered that the claimed Omp A having the sequence of SEQ ID NO: 2 is the same as OmpA taught by Rauly et al. Similarly, the claimed antigen sequence of one fragment of G protein of RSV (i.e G1` peptide or SEQ ID 74) is the same as G1` epitope taught by Rauly et al. in the absence of evidence to the contrary. It is also considered that Rauly's composition used for enhacing immunity in a mammal (i.e. human vaccination) having the same name, structural properties, produced from the same organism, in the same institute (Pierre Fabre) by the same group of scientists (Rauly, Haeuw and Baussant) must has been prepared by the same techniques using the same reagents as claimed by the applicants in the absence of evidence to the contrary. However, the use of detergents such as Zwittergent and techniques such as genetic recombination are well within the level of one skilled in the art and would be a matter of optimization of experimental

parameters.

Rauly et al. do not teach intranasal administration.

Cooper et al. teach intranasal administration of *Klebsiella pneumoniae* antigens in mice to induce an immune response (see abstract).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the methods of Rauly et al. and Cooper et al. to obtain a method of improving immunity of a mammal with respect to an antigen or a hapten, through intranasal administration of a pharmaceutical composition comprising *Klebsiella pneumoniae* outer membrane protein OmpA having SEQ ID NO 2. combined with the antigen or the hapten.

Note: Applicants on a response submitted on 7/30/2004 state that an incomplete copy of the Cooper et al. reference was received by the applicants. The examiner respectfully apologizes for any inconvenience, while the examiner had submitted the full document with the office action. A copy of the article is attached to this office action.

In response on 7/30/2004, applicants argue:

a) The office basis for the motivation to combine Rauly and Cooper references are improper, and the office has used impermissible hindsight reasoning by using the applicants' teaching as a blueprint to hunt through the prior art for the claimed elements and combine them as claimed. In response to applicants' argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071,

5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Also in response to applicants' argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In this case, One of ordinary skill in the art would have been motivated to administer the pharmaceutical composition of Rauly et al. because Rauly et al. teach that rP40 is a promising new carrier protein for human vaccination (i.e. vaccination include any route of administration including intranasal), one of ordinary skill in the art would have been further motivated by the teachings of Cooper et al. that protection from disease also follows after intranasal immunization of *Klebsiella pneumoniae* and antibodies develop after intranasal immunization. Therefore, using Rauly' protein obtained by recombinant process intranasally as taught by Cooper et al. would have improved immunity.

b) Applicants further argue that Cooper et al. actually teach away from the claimed method of improving immunity because "Low levels of antibodies develop in serum after intranasal immunization". In contrast to the teaching of prior art, the instant invention provides an unexpectedly enhanced capacity to achieve a serum antibody response through intranasal immunization.

Applicants' argument is not found persuasive.

The instant claims are drawn to a method of improving immunity of a mammal with respect to an antigen or hapten, through intranasal administration of a pharmaceutical composition comprising, *Klebsiella pneumoniae* membrane protein OmpA having the sequence SEQ ID NO: 2, combined with the antigen or the hapten.

The instant claims do not restrict the level of immunity, only define the level as "improved", nor is type of immunity restricted to any organ or fluid. Therefore, an immune response induced in a mammal meets the criterion of improvement if the response is more than prior to the administration of antigen/OmpA. Likewise, improved immunity may be evidenced by increased cell mediated immunity or antibody levels in any organ or fluid in the recipient mammal.

Cooper et al teach that mice receiving intranasal administration of a pharmaceutical composition comprising glutaraldehyde-killed *Klebsiella pneumoniae* demonstrated: 1) improved immunity to challenge with relatively high numbers of live *Klebsiella pneumoniae* (398-991 organisms = LD_{50}) compared to controls animals which were invariably susceptible to LD_{50} of fewer than five organisms (Table 1); and, 2) higher concentrations of immunoglobulins in the lung secretions compared to control animals.

Rauly et al teach that a particular outer membrane protein, OmpA of *Klebsiella pneumoniae* when combined with an antigen/hapten generated a strong antibody response without an epitopic suppression in mice preimmunized with rP40, compared to a gold standard reference, tetanus toxoid.

Thus, it would have been obvious to one of skill in the art based upon the teachings of Cooper et al to improve the immune response of a mammal by utilizing the intranasal administration of the composition.

Cooper et al. page 314, recites that " As the extremely good protection produced by the local immunization did not appear to be related to serum antibody titers." Cooper et al. pages 314-315 further recite 'The total antibody level detectable by ELISA in pulmonary secretions of mice immunized intranasally was 32 fold higher than those of mice immunized iv." Cooper et al. page 316, recites " The results in the present report suggest that passively administered IgA mediates significant protection against a highly virulent pathogen of the lung, *Klebsiella pneumoiae.*" Therefore, Cooper et al. do not teach away from the claimed invention, in contrast Cooper et al. teach improving immunity through intranasal immunization.

Conclusion

8. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol S Shahnan-Shah whose telephone number is (571)-272-0863. The examiner can normally be reached on 7:30am-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette F Smith can be reached on (571)-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Khatol Shahnan-Shah, BS, Pharm, MS

Biotechnology Patent Examiner
Art Unit 1645
November 4, 2004

RODNEY P SWARTZ, PH.D
PRIMARY EXAMINER